

REMARKS

In this amendment, claim 20 is amended, claims 1-4 and 24 are canceled, and claims 25-27 are new. After entry of this Amendment, which is respectfully requested, claims 20 and 25-27 are all the claims pending in the application.

The amendments to claim 20 are supported, for example, by claim 24.

New claim 25 is supported, for example, by original claim 2.

New claim 26 is supported, for example, by original claim 3.

New claim 27 is supported, for example, by original claim 4.

Applicants assert that no new matter has been added, and applicants respectfully request that the Amendment be entered.

I. Objections to the Specification

The specification is objected to because the SV40 T antigen-originated nuclear transport signal disclosed at page 25, line 1 of the specification, is not listed in the Sequence Listing submitted March 11, 2003. Thus, the Examiner has issued a Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, a Response to which is due within the time set to respond to the February 9, 2004 Office Action, including extensions of time under 37 C.F.R. § 1.136.

In response, Applicants provide, attached hereto, a Substitute Sequence Listing that includes the SV40 T antigen-originated nuclear transport signal (Ala Pro Lys Lys Lys Arg Lys Val Gly) as SEQ ID NO: 24. Applicants also provide, attached hereto: (1) a Computer Readable

Form of the Substitute Sequence Listing; (2) Response to Notice to Comply With Requirements for Patent Applications Containing Nucleotide Sequences and/or Amino Acid Sequence Disclosures; and (3) a Statement to Support Filing and Submission In Accordance With 37 C.F.R. §§ 1.821-1.825. Applicants believe this Response to be in full compliance with the Examiner's Requirement, and respectfully request that this objection be withdrawn.

In addition, Applicants have herein amended the specification to indicate that the SV40 T antigen-originated nuclear transport signal is SEQ ID NO: 24.

II. Claim Rejections

(1) Claim 1 is rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 5,972,889 to Zychlinsky. Specifically, the Examiner states that Zychlinsky teaches a GAL4 responsive element and a promoter, as well as a Fas antigen that inherently has transmembrane and apoptosis-inducing domains. The Examiner states that Zychlinsky teaches that both Fas and IpaB induce apoptosis through ICE, and are therefore, according to the Examiner, functional equivalents. The Examiner states that Zychlinsky teaches a means for inducing apoptosis in a controlled manner using an IpaB DNA construct with an estrogen-inducible system that is controlled by a GAL4 responsive promoter transactivated in the presence of a steroid ligand by a fusion protein that comprises a GAL4 DNA-binding domain and the ligand-binding domain of an estrogen receptor. Thus, the Examiner concludes that the only difference between Zychlinsky and the present plasmid construct is the apoptosis-causing peptide.

(2) Claims 1-4 are rejected under 35 U.S.C. § 103(a) as obvious over Zychlinsky, in view of any one of Oehm *et al.* (1992), Adach *et al.* (1993), or Itoh *et al.* (1991). Specifically,

the Examiner states that Oehm, Adach, and Itoh teach SEQ ID NOS: 22 and 23. The Examiner further states that one of ordinary skill in the art would have been motivated to make the present plasmid construct because Zychlinsky teaches its utility for inducing apoptosis, and teaches that IpaB and Fas are functional equivalents for inducing apoptosis. Thus, the Examiner concludes that it would have been obvious to replace IpaB in the construct of Zychlinsky with SEQ ID NOS: 22 or 23 as taught by Oehm, Adach, and Itoh.

(3) Claims 1, 20, and 24 are rejected under 35 U.S.C. § 103(a) as obvious over Zychlinsky, in view of Braselmann *et al.* (1993). Specifically, the Examiner states that Braselmann teaches a plasmid encoding a fusion protein that comprises a GAL4 DNA binding domain and a nuclear receptor ligand-binding domain (amino acids 281 to 595 of human estrogen receptor). The Examiner further contends that Braselmann teaches that the hormone-binding region of human estrogen receptor can be used, via a fusion with the GAL4 DNA-binding domain, to stimulate transcription from a GAL4-responsive gene in a hormone-dependent manner. Therefore, the Examiner concludes that it would have been obvious to make a plasmid to activate apoptosis by activating transcription of Fas controlled by a fusion protein comprising the GAL4 DNA binding domain and a nuclear receptor ligand-binding region.

(4) Claims 1, 20 and 24 are rejected under 35 U.S.C. § 103(a) as obvious and over Zychlinsky in view of Braselmann, and further in view of the instant specification at the paragraph bridging pages 11-12. Specifically, the Examiner contends that the specification at page 11-12 admits that the ligand-binding region of each receptor recited in claim 24 was known in the art. Therefore, the Examiner contends that it would have been obvious to make the transcriptional induction construct by fusing GAL4 DNA binding region to another nuclear

receptor ligand-binding region, since Braselmann suggests that a nuclear receptor ligand-binding region is useful for regulating transcription and Zychlinsky teaches controlling apoptosis through transcription of an apoptosis-inducing protein encoding gene.

III. Response to Rejections

Applicants have canceled claims 1-4 and 24.

Regarding claim 20, Applicants assert that the invention defined by such has unexpectedly superior properties, and is therefore not obvious over the cited art.

When the nuclear receptor ligand binding regions recited in part (b) of claim 20 are used to induce cell death in a ligand-dependent manner, Fas induced cell death occurs in a dose-dependent manner. This unexpected property is disclosed in Example 6 of the specification (see last paragraph of page 29 and page 32; see Figures 1-4).

Dose dependency allows an investigator to better screen for agonists of each rectied nuclear receptor using Fas induced cell death as the index, since Fas-induced cell death better correlates to the potency of the ligand. In addition, dose dependency allows the investigator to use the composition as a therapeutic agent. For example, by introducing the composition into a cancer cell, and administering the discretionional agonist to the cell, cell death can be controlled by the dose of the administered agonist.

The dose-dependent nature of the invention depends on the following criteria: (1) the activation ability of the agonist-bound fusion protein, (2) the amount of Fas expressed by the binding of the agonist-bound fusion protein to the GAL4 responsive element, and (3) the activity

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of the expressed Fas antigen. Thus, dose dependency of any construct cannot be predicted nor easily obtained based on the teachings of cited prior art alone or in combination.

Applicants assert that claims 20 and 25-27 are not obvious over the cited art, and Applicants respectfully request withdrawal of this rejection.

IV. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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